Remarks

In the Office Action mailed July 29, 2004, the Examiner rejected claims 10-15, 25, 27, 32-34, 66-68, 70 and 71 under U.S.C. § 112, second paragraph, for indefiniteness and under U.S.C. § 112, first paragraph, for lack of enablement. The specific grounds for objection and Applicants' response thereto are set out in detail below.

Claims 10-14, 25, 27, and 32 have been amended and claim 72 has been added. Claims 10-15, 25, 27, 32-34, 66-68, and 70-72 are pending for consideration, which is respectfully requested in view of the foregoing claim amendments and the following remarks. Support for the amendments to claim 10 is located at page 10, line 10 to page 11, line 10 and in SEQ. ID No. 2. Support for added claim 72 is located at page 19, line 15 to page 20, line 25 and in SEQ. ID NOs. 10, 12 and 13.

Rejection under § 112, second paragraph

The Examiner rejects claims 10-15, 25, 27, 32-34, 66-68, 70 and 71 for the alleged reason that the claims are indefinite for failing to distinctly claim the subject matter that the Applicants regard as their invention. Specifically, the Examiner rejects claim 10 for reciting "mutant *ras* peptide comprising an amino acid sequence of at least 8 to no more than 13 amino acids." The Examiner also alleges claim 10 is internally inconsistent because the term "comprising" is open-ended yet the claim also recites that the upper length of the claimed amino acid sequence is limited "to no more than 13 amino acids." Applicants respectfully traverse.

Applicants submit that one skilled in the art would fully appreciate the *ras* mutant peptides encompassed by the scope of claims 10-15, 25, 27, 32-34, 66-68, 70 and 71 by employing no more than routine experimentation. Nevertheless, without acquiescing in any way in the propriety of the rejection, Applicants have amended claim 10 to include recitation of the motif of " Xaa_1 Leu Xaa_2 Val Val Gly Ala Xaa_3 Gly Val Gly Lys Ser". This change addresses the Examiner's concern that the upper length of the claimed amino acid sequence is limited "to no more than 13 amino acids," thereby rendering the rejection moot. Applicants also have amended claim 10 to replace the term "comprising" with "consisting of", thereby addressing the second part of the Examiner's rejection. Accordingly, withdrawal of the entire § 112, second paragraph, rejection respectfully is requested.

Rejection under § 112, first paragraph

The Examiner has maintained the rejection that "a mutant *ras* peptide comprising (or having) the sequence YLVVVGADGV" is not enabled. Specifically, the Examiner alleges that a peptide must be 8-10 amino acids in length to elicit a $CD8^+$ cytotoxic T cell response. Applicants respectfully disagree.

In reply to the Examiner's assertion, Applicants submit appendices A-E (attached hereto), which are published manuscripts demonstrating that peptides longer than 8-10 amino acids can bind MHC class I. Specifically, each of these references demonstrates the use of 13-mer peptides in human and murine *in vivo* and *in vitro* studies. Applicants respectfully request that the Examiner review these articles and withdraw the rejection.

The Examiner also newly rejects claims 10-15, 25, 27, 32-34, 66-68, 70 and 71, asserting the following:

(1) The specification is not enabling for how to use the peptides comprising the instant motif in cancer immunotherapy as contemplated on page 2, lines 29-31. Specifically, the Examiner contends "without evidence that the mutations encompassed by the *ras* peptides of the instant claims were present on human tumor cells, one of skill in the art would not expect the $CD8^+$ T cells elicited thereby to induce lysis of tumor cells *in vitro*"; and

(2) The specification is not enabling for how to use the instant peptides to induce an immune response *in vivo*, to constitute an anti-cancer immunotherapy. She alleges "the state of the art with respect to treating patients with cancer by means of administering tumor antigen precursors or tumor antigens is unpredictable"; and

(3) The specification does not provide any disclosure that the administration of the claimed polypeptides would generate CTLs which lyse the cells of a tumor *in situ* or that tumor cells in a patient would harbor all of the variant K-*ras* peptides claimed. Applicants respectfully traverse each of these assertions.

One skilled in the art would readily be able to determine and generate all of the *ras* mutant peptides encompassed by the scope of claims 10-15, 25, 27, 32-34, 66-68, 70, 71 and new claim 72 by employing no more than routine experimentation. Specifically, Appendix C - "*Induction of Human Cytotoxic T Cell Lines Directed Against Point-Mutated p21 Ras-Derived Synthetic Peptides*" provides evidence that not only did one of skill in the art expect that the

mutant *ras* peptides are capable of inducing $CD8^+$ T cells effective to induce lysis of tumor cells *in vitro*", but in fact lysis of human tumor cells by *ras* mutant peptides-specific $CD8^+$ T cells was achieved (*see* Figures 3 and 4 and Discussion).

Applicants further submit that the specification fully enables one of skill in the art to use the claimed mutant *ras* peptides to induce an *in vivo* immune response, thereby constituting an anti-cancer immunotherapy. Applicants direct the Examiner to appendicies A and B, which both provide evidence of the utility of the claimed invention *in vivo*. Appendix A, entitled "*A Phase I Vaccine Trial With Peptides Reflecting ras Oncogene Mutations of Solid Tumors*," demonstrates the use of a 13-mer mutated *ras* peptide in phase I clinical trials for the treatment of cancer. Appendix B, entitled. "*Generation of Stable $CD4^+$ and $CD8^+$ T Cell Lines from Patients Immunized with ras Oncogene-Derived Peptides Reflecting Codon 12 Mutations*," demonstrates the utility of *ras*-oncogene derived peptides in a peptide-based phase I immunotherapy trial in metastatic carcinoma patients harboring K-*ras* codon 12 mutations. Contrary to the Examiner's assertions, the state of the art with respect to treating cancer patients by means of administering tumor antigen precursors or tumor antigens is not unpredictable.

Regarding the Examiner's assertion that there is no enablement for the teaching that the administration of the claimed polypeptides would generate CTLs that lyse the cells of a tumor *in situ* or that tumor cells in a patient would harbor all of the variant K-*ras* peptides claimed, Applicants direct the Examiner to appendicies A-E. Specifically, the discussion and figures 2, 3, and 5, and the discussion of appendix B describe in detail how mutant *ras* peptides can elicit a therapeutic *ras* peptide-specific $CD8^+$ T cell response. Applicants also submit that figures 1-4 and the discussion of appendix A provide sufficient evidence to support their teaching that the claimed *ras* peptide would elicit a $CD8^+$ T cell response to a variety of mutant *ras* peptides. (*see* appendix A at page 163, second column, second full paragraph).

For all of the above stated reasons, Applicants request that the Examiner withdraw the § 112, first paragraph rejection.

CONCLUSION

In view of the above remarks and amendments, Applicants respectfully submit that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

If any additional fees are required for the filing of this paper, Applicants authorize the Commissioner to charge any deficiency to Deposit Account No. 08-1641.

Respectfully submitted,

Date: October 29, 2004

By _____

Shawnmarie Mayrand-Chung
Agent for Applicants
Registration No. 48,986

Customer No. 44991
HELLER EHRMAN WHITE &
MCAULIFFE LLP
1666 K Street, N.W., Suite 300
Washington, DC 20006
Telephone: (202) 912-2000
Facsimile: (202) 912-2020